REMARKS

Claims 37-48 remain pending in the present application.

As a preliminary matter, Applicants include herewith a Supplemental Information Disclosure Statement.

I. Obviousness-Type Double Patenting

Claims 37-48 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-27 of U.S. Patent No. 6,258,540. Applicants traverse this rejection and respectfully request reconsideration because the Office Action has not presented a *prima facie* case of obvious.

The Office Action on page 10 summarizes the language recited in the claims of the present application and the claims of U.S. Patent No. 6,258,540 and simply concludes, without any analysis, that the conflicting claims are not patentably distinct from one another. The patent laws, however, require more than a mere overlap in claim scope when concluding that particular compounds are obvious variants. As stated by the Federal Circuit:

> The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. (citation omitted)

In re Baird, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). As stated in §804 of the M.P.E.P., the analysis employed in an obvious-type double patenting determination parallels the guidelines for analysis of a 35 U.S.C. §103 rejection, which requires analysis of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). No such analysis has been carried out in the Office Action.

In addition, obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double

patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804. A determination whether one patent application is generic to another patent application is not the appropriate inquiry. The following quotation from *In re Kaplan*, 229 U.S.P.Q. 678 (Fed. Cir. 1986) is instructive:

> By domination we refer ... to that phenomenon ... whereunder one patent has a broad or "generic" claim which "reads on" an invention defined by another narrower or more specific claim in another patent, the former "dominating" the latter because the more narrowly claimed invention cannot be practiced without infringing the broader claim ... In possibly, simpler terms, one patent dominates another if a claim of the first patent reads on a device built or process practiced according to the second patent disclosure. This commonplace situation is not, *per se*, double patenting as the board seems to think. (citations omitted).

Thus, that some of Applicants' claimed methods in the present patent application may also be broader than claims in another patent is not grounds for an obviousness-type double patenting rejection. It is simply a case of one patent dominating another patent. Domination by itself cannot support a double patenting rejection. Thus, the obviousness-type double patenting rejection is misplaced.

To advance prosecution of the present application, however, Applicants will file a Terminal Disclaimer in response to an indication of allowable subject matter. In view of the foregoing, Applicants respectfully request that the obviousness-type double patenting rejection be withdrawn.

II. The Claimed Invention Is Sufficiently Enabled

Claims 37-48 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action asserts that although methods of detecting paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female are enabled, methods of performing the same procedure to detect a nucleic acid that is associated with a genetic trait, condition or abnormality not present in the pregnant female are not enabled. The Office Action mistakenly concludes that it would require undue experimentation to determine whether the detected nucleic acid was a result of the maternal DNA found in the maternal plasma or serum or whether the detected nucleic acid was from the fetus.

Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

The thrust of the reasoning for the enablement rejection set forth in the Office Action appears to be based upon a misconception of the claim language. The Office Action asserts that a "pregnant female may be a carrier or [sic] a nucleic acid associated with a genetic trait" such as diabetes, hair color, or schizophrenia in which two copies of the gene are necessary for phenotypic

expression. If such a pregnant female possesses only one copy of the gene in her genome, although she will not demonstrate the phenotypic expression, she has the potential to possess the nucleic acid molecule in her plasma or serum. Thus, a nucleic acid molecule that is detected in the maternal plasma or serum in such a pregnant female cannot for certain be identified as being of fetal origin. Applicants' claims 37-40, however, do not encompass this situation. Claim 37, for example, recites that the "genetic trait" is not present in the pregnant female. Indeed, the Office Action has already stated that a pregnant female may be a carrier of a nucleic acid associated with a genetic trait (i.e., she has a single copy of a recessive gene). If the female is a carrier of a gene associated with a genetic trait, then the nucleic acid associated with the genetic trait **is present** in the pregnant female. Such a pregnant female is explicitly excluded from claims 37-40 (i.e., "not present" in the pregnant female).

In those claims directed to aneuploidy, although the pregnant female may contain one copy of a gene or chromosome for that matter, the corresponding fetal DNA is present in an amount that is different that that of the pregnant female. That is, the fetal DNA may have a different copy number (i.e., may have one or more extra copies of chromosomes or one or more less copies of a chromosome).

Applicants' specification nowhere limits its inventive prenatal diagnostic method to paternally-derived fetal traits. Indeed, Applicants' definition of "prenatal diagnosis" recited in the "Summary and Objects of the Invention" section extends to "fetal abnormalities which may be for example chromosomal aneuploidies or simple mutations." (See, paragraph 0009 of the patent application publication) Further, although the claimed invention is acknowledged by Applicants to be "most useful" for paternally-inherited sequences which are not possessed by the mother, one of ordinary skill in the art would appreciate that the claimed methods can be practiced for the detection of prenatal genetic traits, conditions or abnormalities not present in the mother (i.e., mutations that are neither paternally nor maternally derived) using the methodology described in the application.

One skilled in the art, for example, would understand that the absence of the mutation in the maternal genome is determined by comparison of a maternal nucleic acid sample from the female free of contamination by fetal nucleic acids. This could be accomplished through a variety of routine

procedures well known in the art (e.g., by comparison with a blood sample obtained prior to pregnancy or by comparison with a tissue sample from the pregnant female). Indeed, "pre-conception" sampling is described in Applicants' specification (see, paragraphs 0152 and 0157 of the published application).

The Office Action attempts to support its assertions of non-enablement by referring to three references (each of which, however, was published after Applicants' filing date). Significantly, none of the references teaches or even suggest that Applicants' claimed invention will not work. Indeed, the references do not purport to be reviews of Applicants' claimed invention and are, therefore, irrelevant to the issue of enablement of Applicants' claimed invention.

For example, Amicucci et al., Clin. Chem., 2002, 46, 301-302 is a brief report on a single patient (see end of first paragraph) that concluded (see last paragraph) that the autosomal dominant disorder myotonic dystrophy could possibly be diagnosed in the fetus via sampling of the maternal plasma. The authors' statement that their "test seems appropriate only for monitoring paternally expanded alleles [of myotonic dystrophy]" cannot with any fairness be extrapolated to Applicants' claimed invention. Indeed, Applicants' published patent application is not referenced in this brief article.

Lo (one of the named inventors of the present application), Ann. Med., 1999, 31, 308-312 describes his work in diagnosing fetal rhesus D status by analysis of maternal plasma or serum DNA. The review does not include any discussion of experimental work other than prenatal diagnosis of fetal RhD genotyping. The statement by the author under "Future Directions" on page 310 regarding the possibility of extending the RhD methodology to other single-gene disorders, merely acknowledges the broad application of the approach not only to detection of paternally inherited genes, but also DNA polymorphisms or mutations that are distinguishable from the maternally inherited counterparts. Thus, the Lo reference is irrelevant to the issue of enablement of Applicants' claimed invention.

Pertl et al., Obstetrics & Gynecology, 2001, 98, 483-490 is merely a review of 369 MedLine-searched articles published between January 1970 and March 2000 which mention "fetal DNA", "plasma" and "serum". Although some of the MedLine articles mentioned include inventor

Lo as an author, the focus of this article is a broad view of prenatal diagnosis up until the March 2000 publication cut-off and the authors' conclusions are based on this perspective. The review article adds no substantive information to the issue of enablement of Applicants' claimed invention, particularly since Applicants' US application had not yet been published and since their counterpart international application is not cited.

Thus, none of the three cited references provides any convincing reasons that suggest that Applicants' claimed invention, as defined by pending claims 36-47, is not enabled by the originally-filed specification.

In view of the foregoing, Applicants' claimed methods are clearly enabled by their specification. Thus, there is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation in order to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

III. The Claimed Invention Is Supported by Ample Written Description

Claims 37-48 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed invention.

As stated in the "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1 'Written Description' Requirement,":

> Possession may be shown by actual reduction to practice, by a clear depiction of the invention in detailed drawings which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention, or by a written description of the invention describing sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention.

In accordance with these standards, Applicants have indeed, provided a sufficient written description of the claimed invention.

The Office Action asserts that the phrase "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female" is unsupported by Applicants' specification (emphasis in the original -- see, page 3 of the Office Action). The Office Action further asserts that the specification does not support the concepts of either nucleic acids that differ between maternal genome and fetal genome and spontaneous differences.

The specification does, in fact, provide support for the concept of the recited terminology. By way of illustration, Applicants' definition of "prenatal diagnosis" in the "Summary and Objects of the Invention" section extends to "fetal abnormalities which may be for example chromosomal aneuploidies or simple mutations" (see, paragraph 0009 of the patent application publication). This broad definition in paragraph 9 nowhere limits the "prenatal diagnosis" of this invention to detection of "paternally-derived" traits. Further, this definition nowhere limits the abnormalities to appearing in both the fetus and the pregnant woman. Thus, regarding abnormalities, it is more likely than not that the pregnant female would not have the same abnormality as the fetus. Thus, Applicants' specification clearly contemplates a "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female."

In addition, in Example 2 (paragraphs 0045-0074 of the published patent application), Applicants describe the quantitative analysis of fetal DNA in maternal serum in aneuploidal pregnancies. The results and data in this example, shown graphically in Figure 1, demonstrate that the concentration of fetal DNA is significantly higher in women with aneuploidal pregnancies as compared with normal pregnancies. **The aneuploidal abnormality was not present in the pregnant women studied**. The abnormality, i.e., a chromosomal aneuploidy -- an abnormality that manifests itself in the fetus as a missing or extra chromosome, was present in the fetuses but not in the pregnant females carrying such fetuses. The nucleic acid of interest used in Example 2 was fetal SRY DNA concentration, since the chromosomal aneuploidy manifests itself in higher than "normal" concentrations of fetal DNA, as is shown by the data in Figure 1. In this case, the SRY DNA served as the "nucleic acid of interest", since its abnormal concentration is "associated with the genetic trait

of, condition or abnormality not present in the pregnant female". Consequently, the present specification does indeed disclose and discuss genetic traits, conditions or abnormalities that are not present in the pregnant female herself.

In addition, Applicants' specification nowhere limits its inventive prenatal diagnostic method to paternally-derived fetal traits. The specification does acknowledge that the fetal DNA detection method of this invention would be "most useful" for paternally-inherited sequences which are not possessed by the mother. The specification, however, nowhere explicitly or implicitly limits the inventive method to these situations.

For these reasons, the claim language "nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female" is described and discussed in the specification and does not constitute new matter.

The Office Action also asserts that claims 38, 40, 41, and 45 lack written description support for a "comparison between maternal genome while carrying the fetus and free of contamination by fetal nucleic acids." (See, page 4 of the Office Action). Applicants direct the Examiner's attention to Example 3 in their specification, which concerns the prenatal determination of fetal RhD status. In this Example, genomic DNA was isolated from the buffy coat (white blood cells) isolated during recovery of the plasma sample from the pregnant females to confirm by genotyping that the pregnant females were RhD negative (Paragraphs 0097 and 0085, 0087 of the patent application publication). Thus, a comparison between the maternal plasma and counterpart "maternal nucleic acid sample from the pregnant female free of contamination by fetal nucleic acids" was, in fact, carried out in Example 3.

Further, additional support for the comparisons recited in claims 38, 40-41 and 45 can be found in Example 5, which is directed to quantitative analysis of fetal DNA in maternal plasma and serum. In this Example, a number of pregnant females involved in the study were recruited from an *in vitro* fertilization (IVF) program, and maternal blood samples were obtained from these females prior to conception as well as afterwards (paragraphs 0132, 0152 of the patent application publication). These IVF females were confirmed to be negative for SRY sequences in their sera prior

to conception, and these preconception data points are noted at a zero gestation age in the results shown in Figures 4A-4L.

The Office Action also asserts that claim 46 lacks written description support for an "assay requiring two probes, one to an aneuploidy sequence and one to a non-aneuploidy sequence." (See, page 4 of the Office Action. Applicants direct the Examiner's attention to the "second method" (discussed in paragraph 0020 of the patent application publication) in which the prenatal diagnostic method of this invention may be applied to chromosomal aneuploidies. The method described in paragraph 0020 "involves the quantitation of fetal DNA markers on different chromosomes" and notes that the "absolute quantity of fetal chromosomal 21-derived DNA [which is associated with Down's syndrome] will always be greater that that from the other chromosomes". The reference to "fetal DNA markers" and "other chromosomes" (emphasis added) makes it clear that separate, different probes would be required for identification of the respective chromosomal marker nucleic acids of interest. The subject matter of claim 46 is consequently supported by Applicants' specification.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

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